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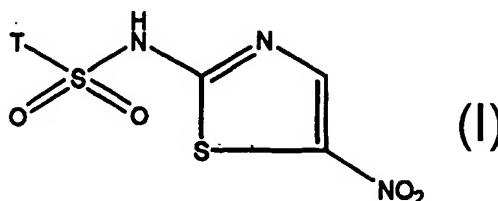
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(54) Title: INHIBITORS OF 11-BETA-HYDROXY STEROID DEHYDROGENASE TYPE 1



(57) Abstract: The present invention relates to compounds
with formula (I) and also to pharmaceutical compositions
comprising the compounds, to processes for their prepara-
tion, as well as to the use of the compounds in medicine and
for the preparation of a medicament which acts on the hu-
man 11- β -hydroxysteroid dehydrogenase type 1 enzyme.

INHIBITORS OF 11-BETA-HYDROXY STEROID DEHYDROGENASE TYPE 1

5 TECHNICAL FIELD

The present invention relates to novel compounds, to pharmaceutical compositions comprising the compounds, to processes for their preparation, as well as to the use of the compounds in medicine and for the preparation of a medicament which acts on the 10 human 11- β -hydroxysteroid dehydrogenase type 1 enzyme (11 β HSD1).

BACKGROUND ART

1. Glucocorticoids, diabetes and hepatic glucose production

15 It has been known for more than half a century that glucocorticoids have a central role in diabetes, e.g. the removal of the pituitary or the adrenal gland from a diabetic animal alleviates the most severe symptoms of diabetes and lowers the concentration of glucose in the blood (Long, C.D. and F.D.W. Leukins (1936) J. Exp. Med. 63: 465-490; Houssay, B.A. (1942) Endocrinology 30: 884-892). It is also well established that 20 glucocorticoids enable the effect of glucagon on the liver.

The role of 11 β HSD1 as an important regulator of local glucocorticoid effect and thus 25 of hepatic glucose production is well substantiated (see e.g. Jamieson et al. (2000) J. Endocrinol. 165: p. 685-692). The hepatic insulin sensitivity was improved in healthy human volunteers treated with the non-specific 11 β HSD1 inhibitor carbenoxolone (Walker, B.R. et al. (1995) J. Clin. Endocrinol. Metab. 80: 3155-3159). Furthermore, the expected mechanism has been established by different experiments with mice and rats. These studies showed that the mRNA levels and activities of two key enzymes in 30 hepatic glucose production were reduced, namely: the rate-limiting enzyme in gluconeogenesis, phosphoenolpyruvate carboxykinase (PEPCK), and glucose-6-

phosphatase (G6Pase) catalyzing the last common step of gluconeogenesis and glycogenolysis. Finally, the blood glucose level and hepatic glucose production is reduced in mice having the 11 β HSD1 gene knocked-out. Data from this model also confirm that inhibition of 11 β HSD1 will not cause hypoglycemia, as predicted since 5 the basal levels of PEPCK and G6Pase are regulated independently of glucocorticoids (Kotelevtsev, Y. et al., (1997) Proc. Natl. Acad. Sci. USA 94: 14924-14929).

2. Possible reduction of obesity and obesity related cardiovascular risk factors

10 Obesity is an important factor in syndrome X as well as in the majority (> 80%) of type 2 diabetic, and omental fat appears to be of central importance. Abdominal obesity is closely associated with glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and other factors of the so-called syndrome X (e.g. raised blood pressure, decreased levels of HDL and increased levels of VLDL) (Montague & 15 O'Rahilly, Diabetes 49: 883-888, 2000). Inhibition of the enzyme in pre-adipocytes (stromal cells) has been shown to decrease the rate of differentiation into adipocytes. This is predicted to result in diminished expansion (possibly reduction) of the omental fat depot, i.e. reduced central obesity (Bujalska, I.J., S. Kumar, and P.M. Stewart (1997) Lancet 349: 1210-1213).

20

Inhibition of 11 β HSD1 in mature adipocytes is expected to attenuate secretion of the plasminogen activator inhibitor 1 (PAI-1) – an independent cardiovascular risk factor (Halleux, C.M. et al. (1999) J. Clin. Endocrinol. Metab. 84: 4097-4105). Furthermore, there is a clear correlation between glucocorticoid “activity” and cardiovascular risk 25 factor suggesting that a reduction of the glucocorticoid effects would be beneficial (Walker, B.R. et al. (1998) Hypertension 31: 891-895; Fraser, R. et al. (1999) Hypertension 33: 1364-1368).

30 Adrenalectomy attenuates the effect of fasting to increase both food intake and hypothalamic neuropeptide Y expression. This supports the role of glucocorticoids in promoting food intake and suggests that inhibition of 11 β HSD1 in the brain might

increase satiety and therefore reduce food intake (Woods, S.C. et al. (1998) *Science*, 280: 1378-1383).

3. Possible beneficial effect on the pancreas

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Inhibition of 11 β HSD1 in isolated murine pancreatic β -cells improves the glucose-stimulated insulin secretion (Davani, B. et al. (2000) *J. Biol. Chem.* 2000 Nov 10; 275(45): 34841-4). Glucocorticoids were previously known to reduce pancreatic insulin release *in vivo* (Billaudel, B. and B.C.J. Sutter (1979) *Horm. Metab. Res.* 11: 10 555-560). Thus, inhibition of 11 β HSD1 is predicted to yield other beneficial effects for diabetes treatment, besides effects on liver and fat.

4. Possible beneficial effects on cognition and dementia

15 Stress and glucocorticoids influence cognitive function (de Quervain, D.J.-F., B. Roozendaal, and J.L. McGaugh (1998) *Nature* 394: 787-790). The enzyme 11 β HSD1 controls the level of glucocorticoid action in the brain and thus contributes to neurotoxicity (Rajan, V., C.R.W. Edwards, and J.R. Seckl, J. (1996) *Neuroscience* 16: 65-70; Seckl, J.R., Front. (2000) *Neuroendocrinol.* 18: 49-99). Unpublished results 20 indicate significant memory improvement in rats treated with a non-specific 11 β HSD1 inhibitor (J. Seckl, personal communication). Based the above and on the known effects of glucocorticoids in the brain, it may also be suggested that inhibiting 11 β HSD1 in the brain may result in reduced anxiety (Tronche, F. et al. (1999) *Nature Genetics* 23: 99-103). Thus, taken together, the hypothesis is that inhibition of 25 11 β HSD1 in the human brain would prevent reactivation of cortisone into cortisol and protect against deleterious glucocorticoid-mediated effects on neuronal survival and other aspects of neuronal function, including cognitive impairment, depression, and increased appetite (previous section).

5. Possible use of immuno-modulation using 11 β HSD1 inhibitors

The general perception is that glucocorticoids suppress the immune system. But in fact there is a dynamic interaction between the immune system and the HPA

5 (hypothalamo-pituitary-adrenal) axis (Rook, G.A.W. (1999) *Baillière's Clin. Endocrinol. Metab.* 13: 576-581). The balance between the cell-mediated response and humoral responses is modulated by glucocorticoids. A high glucocorticoid activity, such as at a state of stress, is associated with a humoral response. Thus, inhibition of the enzyme 11 β HSD1 has been suggested as a means of shifting the response towards

10 a cell-based reaction.

In certain disease states, including tuberculosis, lepra and psoriasis the immune reaction is normally biased towards a humoral response when in fact the appropriate response would be cell based. Temporal inhibition of 11 β HSD1, local or systemic,

15 might be used to push the immune system into the appropriate response (Mason, D. (1991) *Immunology Today* 12: 57-60; Rook et al., *supra*).

An analogous use of 11 β HSD1 inhibition, in this case temporal, would be to booster the immune response in association with immunization to ensure that a cell based

20 response would be obtained, when desired.

6. Reduction of intraocular pressure

Recent data suggest that the levels of the glucocorticoid target receptors and the

25 11 β HSD enzymes determines the susceptibility to glaucoma (Stokes, J. et al. (2000) *Invest. Ophthalmol.* 41: 1629-1638). Further, inhibition of 11 β HSD1 was recently presented as a novel approach to lower the intraocular pressure (Walker E. A. et al, poster P3-698 at the Endocrine society meeting June 12-15, 1999, San Diego).

Ingestion of carbenoxolone, a non-specific inhibitor of 11 β HSD1, was shown to
30 reduce the intraocular pressure by 20% in normal subjects. In the eye, expression of 11 β HSD1 is confined to basal cells of the corneal epithelium and the non-pigmented

epithelialium of the cornea (the site of aqueous production), to ciliary muscle and to the sphincter and dilator muscles of the iris. In contrast, the distant isoenzyme 11 β HSD2 is highly expressed in the non-pigmented ciliary epithelium and corneal endothelium. None of the enzymes is found at the trabecular meshwork, the site of 5 drainage. Thus, 11 β HSD1 is suggested to have a role in aqueous production, rather than drainage, but it is presently unknown if this is by interfering with activation of the glucocorticoid or the mineralocorticoid receptor, or both.

7. Reduced osteoporosis

10

Glucocorticoids have an essential role in skeletal development and function but are detrimental in excess. Glucocorticoid-induced bone loss is derived, at least in part, via inhibition of bone formation, which includes suppression of osteoblast proliferation and collagen synthesis (Kim, C.H., S.L. Cheng, and G.S. Kim (1999) *J. Endocrinol.*

15 162: 371-379). The negative effect on bone nodule formation could be blocked by the non-specific inhibitor carbenoxolone suggesting an important role of 11 β HSD1 in the glucocorticoid effect (Bellows, C.G., A. Ciaccia, and J.N.M. Heersche, (1998) *Bone* 23: 119-125). Other data suggest a role of 11 β HSD1 in providing sufficiently high levels of active glucocorticoid in osteoclasts, and thus in augmenting bone resorption 20 (Cooper, M.S. et al. (2000) *Bone* 27: 375-381). Taken together, these different data suggest that inhibition of 11 β HSD1 may have beneficial effects against osteoporosis by more than one mechanism working in parallel.

WO 99/65884 discloses carbon substituted aminothiazole inhibitors of cyclin dependent 25 kinases. These compounds may e.g. be used against cancer, inflammation and arthritis. US 5,856,347 discloses an antibacterial preparation or bactericide comprising 2-aminothiazole derivative and/or salt thereof. Further, US 5,403,857 discloses benzenesulfonamide derivatives having 5-lipoxygenase inhibitory activity. Additionally, tetrahydrothiazolo[5,4-c]pyridines are disclosed in: Analgesic 30 tetrahydrothiazolo[5,4-c]pyridines. Fr. Addn. (1969), 18 pp, Addn. to Fr. 1498465. CODEN: FAXXA3; FR 94123 19690704 CAN 72:100685 AN 1970:100685 CAPLUS

and 4,5,6,7-Tetrahydrothiazolo[5,4-c]pyridines. Neth. Appl. (1967), 39 pp. CODEN: NAXXAN NL 6610324 19670124 CAN 68:49593, AN 1968: 49593 CAPLUS.

FR 2384498 discloses thiazolo-benzenesulfonamides which show antibacterial, 5 antifungal and hypoglycaemic properties. WO99/28306 and EP 0 819 681 A2 relate to thiazolobenzenesulfonamides which can be used for treating neurodegenerative pathologies, such as Alzheimer's disease. JP 7149745 A2 and JP 7149746 A2 both describe 2-aminothiazole derivatives as esterase inhibitors. Nothing is disclosed about inhibiting 11 β HSD1. JP 7309757 A2 relates to treating Alzheimer's disease using N- 10 (5-nitro-2-thiazolyl)benzenesulfonamides. JP 3173876 A2 presents preparation of diphenylthiazoles. These compounds are used as anti-inflammatories, analgesics, anti-allergy agents, uric acid accelerators and blood platelet aggregation inhibitors. EP 0 790 057 A1 discloses an antibacterial or bactericide comprising a 2-aminothiazole derivative. US 2 362 087 describes the preparation of thiazolobenzenesulfonamides, 15 such as 2-bromobenzenesulfonamido-4-methylthiazole. Nothing is disclosed about inhibiting 11 β HSD1 and no therapeutic use of such substances is disclosed.

However, none of the above disclosures discloses the compounds according to the present invention, or their use for the treatment of diabetes, obesity, glaucoma, 20 osteoporosis, cognitive disorders, immune disorders, and depression.

Consequently, there is a need of new compounds that are useful in the treatment of diabetes, obesity, glaucoma, osteoporosis, cognitive disorders, immune disorders, and depression.

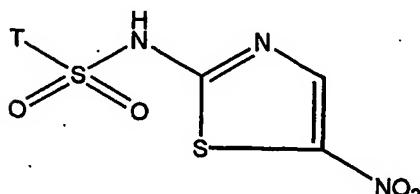
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DISCLOSURE OF THE INVENTION

The compounds according to the present invention solve the above problems and embraces a novel class of compounds which has been developed and which inhibit the 30 human 11- β -hydroxysteroid dehydrogenase type 1 enzyme (11- β -HSD₁), and may

therefore be of use in the treating disorders such as diabetes, obesity, glaucoma, osteoporosis, cognitive disorders, immune disorders, and depression.

One object of the present invention is a compound of the formula (I)



5

wherein T is an aryl ring, substituted with at least one of C₁₋₆-alkyl, halogen, aryl or aryloxy, wherein the aryloxy residue can be further optionally substituted in one or more positions independently of each other by cyano and halogen;

10 with the proviso that T is not 4-methylphenyl, 4-tert-butylphenyl, 4-chlorophenyl, and 4-fluorophenyl;

as well as pharmaceutically acceptable salts, hydrates and solvates thereof.

15 It is preferred that T is phenyl substituted with one or more of chloro, 3-chloro-2-cyanophenoxy, methyl, phenyl and n-propyl; with the proviso that T is not 4-methylphenyl and 4-chlorophenyl.

When T is a substituted phenyl group, it is preferred that the phenyl ring is substituted
20 with at least one of n-propyl, phenyl and 3-chloro-2-cyanophenoxy and, in o- or m-position, methyl and chloro.

Specific examples of compounds according to the invention are:

25 4-(3-chloro-2-cyanophenoxy)-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide;
3-chloro-2-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide;

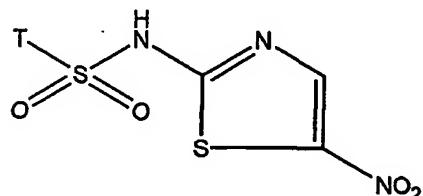
N-(5-nitro-1,3-thiazol-2-yl)[1,1'-biphenyl]-4-sulfonamide;
 N-(5-nitro-1,3-thiazol-2-yl)-4-n-propylbenzenesulfonamide;
 N-(5-nitro-1,3-thiazol-2-yl)-2,4,6-trichlorobenzenesulfonamide;
 2,4-dichloro-6-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide.

5

Another object of the present invention is a compound of the formula (I) as described above for medical use.

Another object of the present invention is a process for the preparation of a compound
 10 as described above comprising sulfonamide coupling by reacting a 2-aminothiazole derivative with a sulfonylchloride in the presence of a base.

Another object of the present invention is a method for the treatment or prevention of diabetes, syndrome X, obesity, glaucoma, hyperlipidemia, hyperglycemia,
 15 hyperinsulinemia, osteoporosis, tuberculosis, depression, virus diseases and inflammatory disorders, said method comprising administering to a mammal, including man, in need of such treatment an effective amount of a compound of the formula (I)



20

wherein T is an aryl ring, optionally independently substituted by [R]_n, wherein n is an integer 0-5, and R is hydrogen, C₁₋₆-alkyl, halogen, aryl or aryloxy, wherein the aryloxy residue can be further optionally substituted in one or more positions independently of each other by cyano and halogen;

25

as well as pharmaceutically acceptable salts, hydrates and solvates thereof.

These compounds may also be used in the manufacture of a medicament for the prevention, management or treatment of diabetes, syndrome X, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, depression, virus diseases and inflammatory disorders.

5

It is preferred that T is phenyl substituted with one or more of chloro, 3-chloro-2-cyanophenoxy, methyl, phenyl and n-propyl.

Specific examples of compounds according to the invention are:

- 10 4-(3-chloro-2-cyanophenoxy)-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide, 3-chloro-2-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide, N-(5-nitro-1,3-thiazol-2-yl)[1,1'-biphenyl]-4-sulfonamide, 4-chloro-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide, N-(5-nitro-1,3-thiazol-2-yl)-4-n-propylbenzenesulfonamide,
- 15 N-(5-nitro-1,3-thiazol-2-yl)-2,4,6-trichlorobenzenesulfonamide, 2,4-dichloro-6-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide.

Another object of the present invention is a pharmaceutical composition comprising at least one compound of the formula (I) as defined above, and a pharmaceutically acceptable carrier.

The compounds according to the present invention may be used in several indications which involve 11- β -hydroxysteroid dehydrogenase type 1 enzyme. Thus the compounds according to the present invention may be used against dementia (see 25 WO97/07789), osteoporosis (see Canalis E 1996, Mechanisms of glucocorticoid action in bone: implications to glucocorticoid-induced osteoporosis, Journal of Clinical Endocrinology and Metabolism, 81, 3441-3447) and may also be used disorders in the immune system (see Franchimont et al, "Inhibition of Th1 immune response by glucocorticoids: dexamethasone selectively inhibits IL-12-induced Stat 4 30 phosphorylation in T lymphocytes", The journal of Immunology 2000, Feb 15, vol 164 (4), pages 1768-74) and also in the above listed indications.

The various terms used, separately and in combinations, in the above definition of the compounds having the formula (I) will be explained.

- 5 The term "aryl" in the present description is intended to include aromatic rings (monocyclic or bicyclic) having from 6 to 10 ring carbon atoms, such as phenyl (Ph) and naphthyl, which optionally may be substituted by C₁₋₆-alkyl. Examples of substituted aryl groups are benzyl and 2-methylphenyl.
- 10 C₁₋₆-alkyl in the compound of formula (I) according to the present application, which may be straight or branched, is preferably C₁₋₄-alkyl. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, isopentyl, hexyl, and isohexyl.
- 15 The term "halogen" in the present description is intended to include fluorine, chlorine, bromine and iodine.

The term "prodrug forms" in the present description means a pharmacologically acceptable derivative, such as an ester or an amide, which derivative is biotransformed in the body to form the active drug (see Goodman and Gilman's, *The Pharmacological basis of Therapeutics*, 8th ed., McGraw-Hill, Int. Ed. 1992, "Biotransformation of Drugs, p. 13-15").

"Pharmaceutically acceptable" means in the present description being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" mean in the present description salts which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with organic

and inorganic acids, such as hydrogen chloride, hydrogen bromide, hydrogen iodide, sulfuric acid, phosphoric acid, acetic acid, glycolic acid, maleic acid, malonic acid, oxalic acid, methanesulfonic acid, trifluoroacetic acid, fumaric acid, succinic acid, tartaric acid, citric acid, benzoic acid, ascorbic acid and the like. Base addition salts 5 may be formed with organic and inorganic bases, such as sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, choline and the like.

10 Pharmaceutical compositions according to the present invention contain a pharmaceutically acceptable carrier together with at least one of the compounds comprising the formula (I) as described herein above, dissolved or dispersed therein as an active, antimicrobial, ingredient. In a preferred embodiment, the therapeutic composition is not immunogenic when administered to a human patient for therapeutic purposes, unless that purpose is to induce an immune response.

15 The preparation of a pharmacological composition that contains active ingredients dissolved or dispersed therein is well understood in the art. Typically such compositions are prepared as sterile injectables either as liquid solutions or suspensions, aqueous or non-aqueous, however, solid forms suitable for solution, or 20 suspensions, in liquid prior to use can also be prepared. The preparation can also be emulsified.

25 The active ingredient may be mixed with excipients, which are pharmaceutically acceptable and compatible with the active ingredient and in amounts suitable for use in the therapeutic methods described herein. Suitable excipients are, for example, water, saline, dextrose, glycerol, ethanol or the like and combinations thereof. In addition, if desired, the composition may contain minor amounts of auxiliary substances such as wetting or emulsifying agents, pH buffering agents and the like which enhance the effectiveness of the active ingredient. Adjuvants may also be present in the 30 composition.

Pharmaceutically acceptable carriers are well known in the art. Exemplary of liquid carriers are sterile aqueous solutions that contain no materials in addition to the active ingredients and water, or contain a buffer such as sodium phosphate at physiological pH value, physiological saline or both, such as phosphate-buffered saline. Still further, 5 aqueous carriers can contain more than one buffer salt, as well as salts such as sodium and potassium chlorides, dextrose, propylene glycol, polyethylene glycol and other solutes.

10 Liquid compositions can also contain liquid phases in addition to and to the exclusion of water. Exemplary of such additional liquid phases are glycerine, vegetable oils such as cottonseed oil, organic esters such as ethyl oleate, and water-oil emulsions.

15 The pharmaceutical composition according to one of the preferred embodiments of the present invention comprising compounds comprising the formula (I), may include pharmaceutically acceptable salts of that component therein as set out above.

20 Pharmaceutically acceptable salts include the acid addition salts (formed with the free amino groups of the polypeptide) that are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic acid, tartaric acid, mandelic acid and the like. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, histidine, procaine and the like.

25 The preparations according to the preferred embodiments may be administered orally, topically, intraperitoneally, intraarticularly, intracranially, intradermally, intramuscularly, intraocularly, intrathecally, intravenously, subcutaneously. Other routes which are known for the skilled person in the art are thinkable.

30 The orally administrable compositions according to the present invention may be in the form of tablets, capsules, powders, granules, lozenges, liquid or gel preparations, such as oral, topical or sterile parenteral solutions or suspensions. Tablets and capsules

for oral administration may be in unit dose presentation form and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, traganath or polyvinyl-pyrrolidone; fillers e.g. lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricant e.g. magnesium stearate, 5 talc, polyethylene glycol or silica; disintegrants e.g. potato starch, or acceptable wetting agents such as sodium lauryl sulfate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of e.g. aqueous or oily suspensions, solutions, emulsions, syrups or elixirs or may be presented as a dry product for reconstitution with water or other 10 suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, e.g. sorbitol, syrup, methyl cellulose, glucose syrup, gelatin hydrogenated edible fats; emulsifying agents e.g. lecithin, sorbitan monooleate or acacia, non-aqueous vehicles (which may include edible oils), e.g. almond oil, fractionated coconut oil, oily esters such as glycerine, propylene glycol, or 15 ethyl alcohol; preservatives e.g. methyl or n-propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

A pharmaceutical composition according to the present invention, may comprise typically an amount of at least 0.1 weight percent of compound comprising the 20 formula (I) per weight of total therapeutic composition. A weight percent is a ratio by weight of total composition. Thus, for example, 0.1 weight percent is 0.1 grams of compound comprising the formula (I) per 100 grams of total composition. A suitable daily oral dose for a mammal, preferably a human being, may vary widely depending on the condition of the patient. However a dose of compound comprising the formula 25 (I) of about 0.1 to 300 mg/kg body weight may be appropriate.

The compositions according to the present invention may also be used veterinarily and thus they may comprise a veterinarily acceptable excipient or carrier.

30 The compounds of the present invention in labelled form, e.g. isotopically labelled, may be used as a diagnostic agent.

The compounds of the formula (I) above may be prepared by, or in analogy with, conventional methods, and especially according to or in analogy with the following methods. Further, the pharmacology in-vitro was studied using the following reagents and methods.

All publications mentioned herein are hereby incorporated by reference. By the expression "comprising" we understand including but not limited to. Thus, other non-mentioned substances, additives or carriers may be present.

10

The invention will now be described in reference to the following Figures and Examples. These Figures and Examples are not to be regarded as limiting the scope of the present invention, but shall only serve in an illustrative manner.

15 EXPERIMENTAL METHODS

Scintillation Proximity Assay

[1, 2(n) - 3 H]-cortisone was purchased from Amersham Pharmacia Biotech. Anti-20 cortisol monoclonal mouse antibody, clone 6D6.7 was obtained from Immunotech and Scintillation proximity assay (SPA) beads coated with monoclonal antimouse antibodies were from Amersham Pharmacia Biotech. NADPH, tetrasodium salt was from Calbiochem and glucose-6-phosphate (G-6-P) was supplied by Sigma. The human 11- β -hydroxysteroid dehydrogenase type-1 enzyme (11- β -HSD₁) was expressed in *Pichia pastoris*. 18- β -glycyrrhetic acid (GA) was obtained from Sigma. The serial dilutions of the compounds were performed on a Tecan Genesis RSP 150. Compounds to be tested were dissolved in DMSO (1 mM) and diluted in 50 mM Tris-HCl, pH 7.2 containing 1 mM EDTA.

The multiplication of plates was done on a WallacQuadra. The amount of the product [³H]-cortisol, bound to the beads was determined in a Packard, Top Count microplate liquid scintillation counter.

5 The 11- β -HSD₁ enzyme assay was carried out in 96 well microtiter plates (Packard, Optiplate) in a total well volume of 220 μ L and contained 30 mM Tris-HCl, pH 7.2 with 1 mM EDTA, a substrate mixture tritiated Cortisone/NADPH (175 nM / 181 μ M), G-6-P (1 mM) and inhibitors in serial dilutions (9 to 0.15 μ M). Reactions were initiated by the addition of human 11- β -HSD₁, either as *Pichia pastoris* cell

10 homogenate or microsomes prepared from *Pichia pastoris* (the final amount of enzyme used was varied between 0.057 to 0.11 mg/mL). Following mixing, the plates were shaken for 30 to 45 minutes at room temperature. The reactions were terminated with 10 μ L 1 mM GA stop solution. Monoclonal mouse antibody was then added (10 μ L of 4 μ M) followed by 100 μ L of SPA beads (suspended according to the

15 manufacturers instructions). Appropriate controls were set up by omitting the 11- β -HSD₁ to obtain the non-specific binding (NSB) value.

The plates were covered with plastic film and incubated on a shaker for 30 minutes, at room temperature, before counting. The amount of [³H]-cortisol, bound to the beads

20 was determined in a microplate liquid scintillation counter.

The calculation of the K_i values for the inhibitors was performed by use of Activity Base. The K_i value is calculated from IC₅₀ and the K_m value is calculated using the Cheng Prushoff equation (with reversible inhibition that follows the Michaelis-Menten 25 equation): K_i = IC₅₀(1+[S]/K_m) [Cheng, Y.C.; Prushoff, W.H. Biochem. Pharmacol. 1973, 22, 3099-3108]. The IC₅₀ is measured experimentally in an assay wherein the decrease of the turnover of cortisone to cortisol is dependent on the inhibition potential of each substance. The K_i values of the compounds of the present invention for the 11- β -HSD₁ enzyme lie typically between about 10 nM and about 10 μ M. The K_i value

30 for the compound according to Example 6 is 545 nM.

METHODS FOR PREPARATION

General:

For preparative straight phase HPLC purification a Phenomenex column (250 x 21.1 mm, 10 μ m) was used on a Gilson system eluting with ethanol in chloroform (gradient from 0 – 10% in 10 min) with a flow of 20 mL/min. Column chromatography was performed on silica using Silica gel 60 (230-400 mesh), Merck. Melting points were determined on a Gallenkamp apparatus. Elemental analyses were recorded using a Vario EL instrument. HPLC analyses were performed using a Hypersil Elite column (150 x 4.6 mm, 3 μ) with a flow of 3 mL / min on a Waters 600E system with monitoring at 254 nm. Reverse phase preparative HPLC was carried out on a 100 x 21.2 mm, 5 μ Hypersil Elite column eluting with a gradient of 5% ACN in 95% water to 95% ACN in 5% water (0.2% TFA buffer) over 10 mins at a flow rate of 20 mL / min with the UV detector set at 254 nm. Thin layer chromatography was carried out using pre-coated silica gel F-254 plates (thickness 0.25 mm). Electrospray MS spectra were obtained on a Micromass platform LCMS spectrometer. Crude, worked up compounds were purified by flash column chromatography using pre packed silica SPE columns (10 g silica) on an Isco Foxy 200 Combiflash system, and a gradient of 16.67% ethyl acetate in hexane increasing incrementally to 100% ethyl acetate.

20

List of Abbreviations:

DMAP = 4-dimethylaminopyridine

DMF = dimethylformamide

DMSO = dimethyl sulfoxide

25 EDTA = ethylenediaminetetraacetic acid

SULFONAMIDE COUPLINGS:

A solution of the 2-aminothiazole derivative (0.27 mmol), triethylamine (0.54 mmol) 30 and DMAP (0.27 mmol) in DMF (250 μ L) and dichloromethane (1.2 mL) was dispensed into a reaction vial. The sulfonyl chloride was dissolved in dichloromethane

(1 mL) and added. The reaction mixtures were kept at room temperature over night. The mixture was then added to petroleum ether (35 mL). After some hours in refrigerator the supernatants were decanted and the residual materials were dissolved in DMSO-methanol-acetic acid (300 μ L + 500 μ L + 50 μ L) and purified by 5 preparative LCMS (acetonitrile-water gradients). The purest fractions were collected and lyophilized. Alternatively, the crude was isolated using extractive work-up and purified using standard procedures.

EXAMPLES

10

The following specific compounds were synthesized.

EXAMPLE 1 [321A]

4-(3-Chloro-2-cyanophenoxy)-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide
15 The title compound was prepared from 2-amino-5-nitrothiazole and 4-(3-chloro-2-cyanophenoxy)benzenesulfonyl chloride as described in the sulfonamide couplings to give a yellow solid (8.7 mg) with purity >90%. LCMS (pos) m/z 437.2.B

EXAMPLE 2 [335A]

20 3-Chloro-2-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide
The title compound was prepared from 2-amino-5-nitrothiazole and 3-chloro-2-methylbenzenesulfonyl chloride as described in the sulfonamide couplings to give a yellow solid (15.2 mg) with purity >90%. LCMS (pos) m/z 332.0.

25 EXAMPLE 3 [336A]

N-(5-nitro-1,3-thiazol-2-yl)[1,1'-biphenyl]-4-sulfonamide

The title compound was prepared from 2-amino-5-nitrothiazole and 4-biphenylsulfonyl chloride as described in the sulfonamide couplings to give a yellow solid (5.5 mg) with purity >90%. LCMS (pos) m/z 362.0.

30

EXAMPLE 4 [337A]**4-Chloro-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide**

The title compound was prepared from 2-amino-5-nitrothiazole and 4-chlorobenzenesulfonyl chloride as described in the sulfonamide couplings to give a 5 yellow solid (19.5 mg) with purity >90%. LCMS (pos) m/z 320.0.

EXAMPLE 5 [338A]**N-(5-nitro-1,3-thiazol-2-yl)-4-n-propylbenzenesulfonamide**

10 The title compound was prepared from 2-amino-5-nitrothiazole and 4-n-propylbenzenesulfonyl chloride as described in the sulfonamide couplings to give a yellow solid (28.5 mg) with purity >90%. LCMS (pos) m/z 328.2.

EXAMPLE 6 [339A]**N-(5-nitro-1,3-thiazol-2-yl)-2,4,6-trichlorobenzenesulfonamide**

15 The title compound was prepared from 2-amino-5-nitrothiazole and 2,4,6-trichlorobenzenesulfonyl chloride as described in the sulfonamide couplings to give a yellow solid (26.7 mg) with purity >90%. LCMS (pos) m/z 389.8; HRMS m/z 386.8718 (calc. of monoisotopic mass for C₉H₄Cl₃N₃O₄S₂ gives 386.8709).

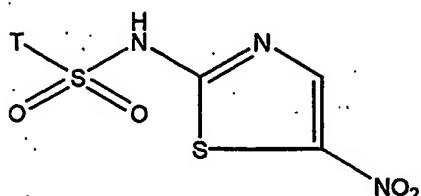
EXAMPLE 7 [340A]**2,4-Dichloro-6-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide**

The title compound was prepared from 2-amino-5-nitrothiazole and 2,4-dichloro-6-methylbenzenesulfonyl chloride as described in the sulfonamide couplings to give a yellow solid (28.4 mg) with purity >80%. LCMS (pos) m/z 368.

25 Various embodiments of the present invention have been described above but a person skilled in the art realizes further minor alterations which would fall into the scope of the present invention. The breadth and scope of the present invention should not be limited by any of the above-described exemplary embodiments, but should be defined 30 only in accordance with the following claims and their equivalents.

Claims

1. A compound of the formula (I)



5

wherein T is an aryl ring, substituted with at least one of C₁₋₆-alkyl, halogen, aryl or aryloxy, wherein the aryloxy residue can be further optionally substituted in one or more positions independently of each other by cyano and halogen;

10 with the proviso that T is not 4-methylphenyl, 4-tert-butylphenyl, 4-chlorophenyl, and 4-fluorophenyl;

as well as pharmaceutically acceptable salts, hydrates and solvates thereof.

15 2. A compound according to claim 1, wherein T is phenyl substituted with one or more of chloro, 3-chloro-2-cyanophenoxy, methyl, phenyl and n-propyl; with the proviso that T is not 4-methylphenyl and 4-chlorophenyl.

3. A compound according to claim 1-2 selected from the group consisting of:

20 4-(3-chloro-2-cyanophenoxy)-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide,
 3-chloro-2-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide,
 N-(5-nitro-1,3-thiazol-2-yl)[1,1'-biphenyl]-4-sulfonamide,
 N-(5-nitro-1,3-thiazol-2-yl)-4-n-propylbenzenesulfonamide,
 N-(5-nitro-1,3-thiazol-2-yl)-2,4,6-trichlorobenzenesulfonamide,
 25 2,4-dichloro-6-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide.

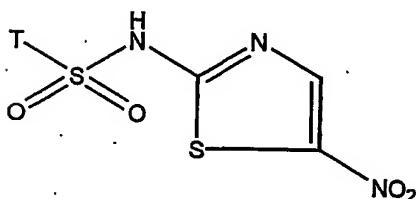
4. A compound according to anyone of claims 1-3, for medical use.

5. A process for the preparation of a compound according to claim 1-3, comprising sulfonamide coupling by reacting a 2-aminothiazole derivative with a sulfonylchloride in the presence of a base.

5

6. A method for the treatment or prevention of diabetes, syndrome X, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, depression, virus diseases and inflammatory disorders, said method comprising administering to a mammal, including man, in need of such treatment an effective amount of a compound of the formula (I)

10



wherein T is an aryl ring, optionally independently substituted by [R]_n, wherein n is an integer 0-5, and R is hydrogen, C₁₋₆-alkyl, halogen, aryl or aryloxy, wherein the 15 aryloxy residue can be further optionally substituted in one or more positions independently of each other by cyano and halogen;

as well as pharmaceutically acceptable salts, hydrates and solvates thereof.

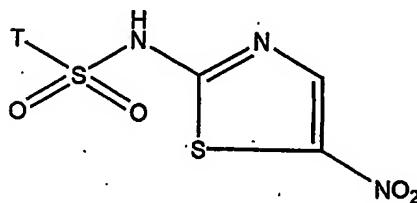
20 7. A method according to claim 6, wherein T is phenyl substituted with one or more of chloro, 3-chloro-2-cyanophenoxy, methyl, phenyl and n-propyl.

8. A method according to claim 6-7, wherein the compound is selected from: 4-(3-chloro-2-cyanophenoxy)-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide, 25 3-chloro-2-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide, N-(5-nitro-1,3-thiazol-2-yl)[1,1'-biphenyl]-4-sulfonamide,

4-chloro-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide,
 N-(5-nitro-1,3-thiazol-2-yl)-4-n-propylbenzenesulfonamide,
 N-(5-nitro-1,3-thiazol-2-yl)-2,4,6-trichlorobzenzenesulfonamide,
 2,4-dichloro-6-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide.

5

9. The use of a compound of the formula (I)



wherein T is an aryl ring, optionally independently substituted by $[R]_n$, wherein n is an integer 0-5, and R is hydrogen, C_{1-6} -alkyl, halogen, aryl or aryloxy, wherein the aryloxy residue can be further optionally substituted in one or more positions independently of each other by cyano and halogen;

as well as pharmaceutically acceptable salts, hydrates and solvates thereof,

15

in the manufacture of a medicament for the prevention, management or treatment of diabetes, syndrome X, obesity, glaucoma, hyperlipidemia, hyperglycemia, hyperinsulinemia, osteoporosis, tuberculosis, depression, virus diseases and inflammatory disorders.

20

10. The use according to claim 9, wherein T is phenyl substituted with one or more of chloro, 3-chloro-2-cyanophenoxy, methyl, phenyl and n-propyl.

11. The use according to claim 9-10, wherein the compound is selected from:

25 4-(3-chloro-2-cyanophenoxy)-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide,
 3-chloro-2-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide,
 N-(5-nitro-1,3-thiazol-2-yl)[1,1'-biphenyl]-4-sulfonamide,

4-chloro-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide,
N-(5-nitro-1,3-thiazol-2-yl)-4-n-propylbenzenesulfonamide,
N-(5-nitro-1,3-thiazol-2-yl)-2,4,6-trichlorobenzenesulfonamide,
2,4-dichloro-6-methyl-N-(5-nitro-1,3-thiazol-2-yl)benzenesulfonamide.

5

12. A pharmaceutical composition comprising at least one compound of the formula (I) as defined in any of the claims 1-3, and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01154

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 277/58, A61K 31/426, A61P 3/00, A61P 5/48, A61P 27/06, A61P 29/00,
A61P 31/12, A61P 31/06 A61P 25/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CHEM.ABS DATA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	STN International, File CHEMCATS, CHEMCATS accession no. 2001:1269188, TimTec Screening Library, 20010219, "Benzene methanesulfonamide, N-(5-nitro-2-thiazolyl)-", RN: 349130-65-0 --	1-3,5
P,X	STN International, File CHEMCATS, CHEMCATS accession no. 2001:1265911, TimTec screening Library, 20010219, "Benzene sulfonamide, 4-bromo-N-(5-nitro-2-thiazolyl)-", RN: 349404-98-4 --	1-3,5
P,X	STN International, File CHEMCATS, CHEMCATS accession no. 2001:1267832, 20010219, "Benzene sulfonamide, 2,4,6-tris(1-methylethyl)-N-(5-nitro-2-thiazolyl)-", RN: 349116-44-5 --	1-3,5

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family
"P" document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search	Date of mailing of the international search report
4 Sept 2001	1.2 -09- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. + 46 8 666 02 86	Authorized officer Gerd Strandell/EÖ Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 01/01154

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	STN International, File CHEMCATS, CHEMCATS accession no. 2001:1268961, TimTec Screening Library, 20010219, "Benzenesulfonamide, 2,4,6-trimethyl-N-(5-nitro-2-thiazolyl)-", RN: 349127-79-3 --	1-3,5
P,X	STN International, File CHEMCATS, CHEMCATS accession no. 2001:1268981, TimTec Screening Library, 20010219, "Benzenesulfonamide, 2,5-dichloro-N-(5-nitro-2-thiazolyl)-", RN: 349127-97-5 --	1-3,5
X	Biol. Pharm. Bull., Volume 18, No 12, 1995, Yasushi Hasegawa et al, "A New Compound (AZ36041) Promotes the Survival of the Neurons and Reduces Neurotoxicity of Alzheimer's Beta-Amyloid Protein" page 1750 - page 1754 --	1-12
X	STN International, File CAPLUS, CAPLUS accession no. 1996:111694, Document no. 124:165271, Asahi Chemical Ind: "Therapeutics for Alzheimer's disease containing N-(5-nitro-2-thiazolyl) benzenesulfonamides"; & JP,A2,07309757, 19951128 --	1-12
X	WO 9747299 A1 (3-DIMENSIONAL PHARMACEUTICALS, INC.), 18 December 1997 (18.12.97), page 49, line 10 - line 16 --	1-3,5
X	STN International, File CAPLUS, CAPLUS accession no. 1983:53154, Document no. 98:53154, Chen, Shicong et al: "Synthesis and schistosomicidal activity of fluoroacetamides - a new class of antischistosomal agents"; & Yaoxue Xuebao (1992), 17(9), 674-81 --	1-12

INTERNATIONAL SEARCH REPORT

International application No. PCT/SE 01/01154
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1980:110111, Document no. 92:110111, Depeshko, I. T. et al: "Electronic structure of bacteriostatically active sulfanilamide derivatives of thiazole"; & Farm. Zh. (Kiev) (1979), 42-5 --	1-12
X	WO 9928306 A1 (PHARMACIA & UPJOHN S.P.A.), 10 June 1999 (10.06.99) --	1-12
A	WO 9707789 A1 (THE UNIVERSITY OF EDINBURGH), 6 March 1997 (06.03.97), claims 9,12 -- -----	1-12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01154

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: **6-8**
because they relate to subject matter not required to be searched by this Authority, namely:
see next sheet
2. Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01154

Claims 6-8 relate to methods of treatment of the human or animal body by surgery or by therapy/ diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT
Information on patent family members

02/08/01

International application No.
PCT/SE 01/01154

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9747299 A1	18/12/97	NONE		
WO 9928306 A1	10/06/99	AU 1753599 A EP 1036069 A GB 9725141 D		16/06/99 20/09/00 00/00/00
WO 9707789 A1	06/03/97	AU 6833796 A EP 0847275 A GB 2317826 A,B GB 9517622 D GB 9801921 D		19/03/97 17/06/98 08/04/98 00/00/00 00/00/00